

**Amendments to the Specification:**

Please replace the paragraph beginning on page 1, line 16 with the following paragraph:

In addition, it is reported that 4-aminobenzopyran derivatives that have  $\beta$ 3-receptor stimulating action and are supposed to be effective for the treatment of obesity ~~compulence~~ (for example, WO 03/014113), but there has not been any mention as to the treatment of arrhythmia based on the prolongation effect on the refractory period this document.

Please replace the paragraph beginning on page 5, line 20 with the following paragraph:

- C<sub>2-9</sub> hetecyclyl group (wherein the heterocyclyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkyl group (wherein the alkyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group), C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), C<sub>6-14</sub> aryl group, C<sub>2-9</sub> heteroaryl group (wherein each of the aryl group or heteroaryl group may be arbitrarily substituted with 1 to 3 R<sup>18</sup> wherein R<sup>18</sup> has the same ~~above-mentioned-meaning as~~ R<sup>10</sup>), hydroxy group, nitro group, cyano group, formyl group, formamide group, amino group, C<sub>1-6</sub> alkylamino group, di-C<sub>1-6</sub> alkylamino group, C<sub>1-6</sub> alkylcarbonylamino group, C<sub>1-6</sub> alkylsulfonylamino group, aminocarbonyl group, C<sub>1-6</sub> alkylaminocarbonyl group, di-C<sub>1-6</sub> alkylaminocarbonyl group, C<sub>1-6</sub> alkylcarbonyl group, C<sub>1-6</sub> alkoxy carbonyl group; aminosulfonyl group, C<sub>1-6</sub> alkylsulfonyl group, carboxy group or C<sub>6-14</sub> arylcarbonyl group);



cycloalkylcarbonyl group, C<sub>1-6</sub> alkoxycarbonyl group, C<sub>1-6</sub> alkylsulfonyl group, carboxy group, C<sub>6-14</sub> arylcarbonyl group or C<sub>2-9</sub> heteroarylcarbonyl group), C<sub>6-14</sub> aryl group, C<sub>2-9</sub> heteroaryl group (wherein each of the aryl group or heteroaryl group may be arbitrarily substituted with 1 to 3 R<sup>19</sup> wherein R<sup>19</sup> has the same meaning as R<sup>10</sup>), C<sub>1-6</sub> alkylaminocarbonyl group, di-C<sub>1-6</sub> alkylaminocarbonyl group, C<sub>1-6</sub> alkylcarbonyl group, C<sub>3-8</sub> cycloalkylcarbonyl group, C<sub>1-6</sub> alkoxycarbonyl group, C<sub>1-6</sub> alkylsulfonyl group, C<sub>6-14</sub> arylsulfonyl group, C<sub>2-9</sub> heteroarylsulfonyl group (wherein each of the arylsulfonyl group or heteroarylsulfonyl group may be arbitrarily substituted with 1 to 3 R<sup>19</sup> wherein R<sup>19</sup> has the same meaning as R<sup>10</sup>), carboxy group; C<sub>6-14</sub> arylcarbonyl group, C<sub>2-9</sub> heteroarylcarbonyl group (wherein each of the arylcarbonyl group or heteroarylcarbonyl group may be arbitrarily substituted with 1 to 3 R<sup>19</sup> wherein R<sup>19</sup> has the same meaning as R<sup>10</sup>), R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> are independently of each other hydrogen atom, halogen atom, C<sub>1-6</sub> alkyl group (wherein the alkyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, hydroxy group, C<sub>6-14</sub> aryl group, C<sub>2-9</sub> heteroaryl group (wherein each of the aryl group or heteroaryl group may be arbitrarily substituted with 1 to 3 R<sup>20</sup> wherein R<sup>20</sup> has the same meaning as R<sup>10</sup>), C<sub>1-6</sub> alkylaminocarbonyl group, di-C<sub>1-6</sub> alkylaminocarbonyl group, C<sub>1-6</sub> alkylcarbonyl group, C<sub>3-8</sub> cycloalkylcarbonyl group, C<sub>1-6</sub> alkoxycarbonyl group, C<sub>1-6</sub> alkylsulfonyl group, carboxy group, C<sub>6-14</sub> arylcarbonyl group or C<sub>2-9</sub> heteroarylcarbonyl group), C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom, (wherein the alkoxy group may be arbitrarily substituted with halogen atom), carboxy group, amino group, hydroxy group, C<sub>6-14</sub> aryl group or C<sub>2-9</sub> heteroaryl group (wherein each of the aryl group or heteroaryl group may be arbitrarily substituted with 1 to 3 R<sup>20</sup> wherein R<sup>20</sup> has the same meaning as R<sup>10</sup>), C<sub>1-6</sub> thioalkoxy group (wherein the thioalkoxy group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkoxy group (wherein the

alkoxy group may be arbitrarily substituted with halogen atom), carboxy group, hydroxy group, C<sub>6-14</sub> aryl group or C<sub>2-9</sub> heteroaryl group (wherein each of the aryl group or heteroaryl group may be arbitrarily substituted with 1 to 3 R<sup>20</sup> wherein R<sup>20</sup> has the same meaning as R<sup>10</sup>), hydroxy group, C<sub>6-14</sub> aryl group or C<sub>2-9</sub> heteroaryl group (wherein each of the aryl group or heteroaryl group may be arbitrarily substituted with 1 to 3 R<sup>20</sup> wherein R<sup>20</sup> has the same meaning as R<sup>10</sup>), C<sub>1-6</sub> alkylcarbonyloxy group, nitro group, cyano group, formyl group, formamide group, amino group, sulfonyl group, C<sub>1-6</sub> alkylamino group, di-C<sub>1-6</sub> alkylamino group, C<sub>6-14</sub> arylamino group, C<sub>2-9</sub> heteroarylamino group (wherein each of the arylamino group or heteroarylamino group may be arbitrarily substituted with 1 to 3 R<sup>20</sup> wherein R<sup>20</sup> has the same meaning as R<sup>10</sup>), C<sub>1-6</sub> alkylcarbonyloxyamino group, C<sub>1-6</sub> alkylsulfonylamino group, aminocarbonyl group, C<sub>1-6</sub> alkylaminocarbonyl group, di-C<sub>1-6</sub> alkylaminocarbonyl group, C<sub>1-6</sub> alkylcarbonyl group, C<sub>6-14</sub> arylcarbonyl group, C<sub>2-9</sub> heteroarylcarbonyl group (wherein each of the arylcarbonyl group or heteroarylcarbonyl group may be arbitrarily substituted with 1 to 3 R<sup>20</sup> wherein R<sup>20</sup> has the same meaning as R<sup>10</sup>), C<sub>1-6</sub> alkoxy carbonyl group, aminosulfonyl group, C<sub>1-6</sub> alkylsulfonyl group, C<sub>6-14</sub> arylsulfonyl group, C<sub>2-9</sub> heteroarylsulfonyl group (wherein each of the arylsulfonyl group or heteroarylsulfonyl group may be arbitrarily substituted with 1 to 3 R<sup>20</sup> wherein R<sup>20</sup> has the same meaning as R<sup>10</sup>), carboxy group, sulfonyl group or C<sub>2-9</sub> heterocyclyl group (wherein the heterocyclyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkyl group (wherein the alkyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group), C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), C<sub>6-14</sub> aryl group, C<sub>2-9</sub> heteroaryl group (wherein each of the aryl group or heteroaryl group may be arbitrarily substituted with 1 to 3 R<sup>20</sup> wherein R<sup>20</sup> has the same ~~above-mentioned~~ meaning as R<sup>10</sup>), hydroxy group, nitro group, cyano group, formyl group, formamide group, amino group,

C<sub>1-6</sub> alkylamino group, di-C<sub>1-6</sub> alkylamino group, C<sub>1-6</sub> alkylcarbonylamino group, C<sub>1-6</sub> alkylsulfonylamino group, aminocarbonyl group, C<sub>1-6</sub> alkylaminocarbonyl group, di-C<sub>1-6</sub> alkylaminocarbonyl group, C<sub>1-6</sub> alkylcarbonyl group, C<sub>1-6</sub> alkoxy carbonyl group, aminosulfonyl group, C<sub>1-6</sub> alkylsulfonyl group, carboxy group or C<sub>6-14</sub> arylcarbonyl group),  
X is O, S, SO or SO<sub>2</sub>;

Please replace the paragraph beginning on page 9, line 7 with the following paragraph:

(8) The benzopyran derivative or pharmaceutically acceptable salt thereof as set forth in (7), wherein R<sup>6</sup> is C<sub>6-14</sub> aryl group wherein the aryl group may be arbitrarily substituted with 1 to 3 halogen atom or amino group, when and when a plurality of substituents are present, they may be identical or different from each other;

Please replace the paragraph beginning on page 9, line 19 with the following paragraph:

(12) The benzopyran derivative or pharmaceutically acceptable salt thereof as set forth in (5), wherein m is an integer of 1 to 3, n is 0, and R<sup>6</sup> is C<sub>2-4</sub> alkyl group (wherein the alkyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group), C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group), C<sub>3-8</sub> cycloalkyl group, C<sub>3-8</sub> cycloalkenyl group (wherein the cycloalkyl group or cycloalkenyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkyl group (wherein the alkyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group), C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen

atom), amino group, carboxy group or hydroxy group), or C<sub>2-9</sub> hetecyclyl group (wherein the heterocyclyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkyl group (wherein the alkyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group), C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), hydroxy group or amino group);

Please replace the paragraph bridging pages 11 and 12 with the following paragraph:

(24) The benzopyran derivative or pharmaceutically acceptable salt thereof as set forth in (15), wherein m is an integer of 1 to 2, n is 0, and R<sup>6</sup> is C<sub>1-4</sub> alkyl group (wherein the alkyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group), C<sub>3-8</sub> cycloalkyl group, C<sub>3-8</sub> cycloalkenyl group (wherein the cycloalkyl group or cycloalkenyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkyl group (wherein the alkyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group), C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group), or C<sub>2-9</sub> hetecyclyl group (wherein the heterocyclyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkyl group (wherein the alkyl group may be arbitrarily substituted with halogen atom, C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group), C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group);

Please replace the paragraph bridging pages 12 and 13 with the following paragraph:

(29) The benzopyran derivative or pharmaceutically acceptable salt thereof as set forth in (15), wherein  $R^7$  and  $R^8$  together are =O or =S, and  $R^6$  is amino group,  $C_{1-6}$  alkylamino group, di- $C_{1-6}$  alkylamino group,  $C_{6-14}$  arylamino group,  $C_{2-9}$  heteroaryl amino (wherein each of the arylamino group or heteroaryl amino group may be arbitrarily substituted with 1 to 3  $R^{18}$  wherein  $R^{18}$  has the same meaning as  $R^{10}$ , or  $C_{2-9}$  heterocyclyl group (wherein the heterocyclyl group may be arbitrarily substituted with halogen atom,  $C_{1-6}$  alkyl group (wherein the alkyl group may be arbitrarily substituted with halogen atom,  $C_{1-6}$  alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group),  $C_{1-6}$  alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group, carboxy group or hydroxy group);

Please replace the paragraph beginning on page 14, line 2 with the following paragraph:

(38) The benzopyran derivative or pharmaceutically acceptable salt thereof as set forth in (37), wherein  $R^{11}$  is hydrogen atom or  $C_{1-6}$  alkyl group (wherein the alkyl group may be arbitrarily substituted with halogen atom,  $C_{1-6}$  alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group or hydroxy group), and  $R^{13}$ ,  $R^{14}$  and  $R^{15}$  are independently of each other hydrogen atom, halogen atom,  $C_{1-6}$  alkyl group (wherein the alkyl group may be arbitrarily substituted with halogen atom,  $C_{1-6}$  alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom) or hydroxy group),  $C_{1-6}$  cycloalkyl group (wherein the cycloalkyl group may be arbitrarily substituted with halogen atom,  $C_{1-6}$  alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom), amino group or hydroxy group),  $C_{1-6}$  ~~alkoxy~~-alkoxy group (wherein the ~~alkoxy~~-alkoxy group may be arbitrarily substituted with halogen atom, amino

group, C<sub>1-6</sub> alkoxy group (wherein the alkoxy group may be arbitrarily substituted with halogen atom) or hydroxy group), C<sub>1-6</sub> alkylcarbonyl group, aminocarbonyl group, amino group, carboxy group or cyano group;

Please replace the paragraph beginning on page 19, line 17 with the following paragraph:

7-chloro-4-[[[2-tetrahydropyran-4-yl)ethyl]amino]]-2,2,9-trimethyl-3,4-dihydro-2H-pyrano[2,3-g]quinolin-3-ol,

Please replace the paragraph bridging pages 23 and 24 with the following paragraph:

Examples of C<sub>3-8</sub> cycloalkyl group are such as c-propyl, c-butyl, i-methyl-c-propyl, 2-methyl-c-propyl, c-pentyl, 1-methyl-c-butyl, 2-methyl-c-butyl, 3-methyl-c-butyl, 1,2-dimethyl-c-propyl, 2,3-dimethyl-c-propyl, 1-ethyl-c-propyl, 2-ethyl-c-propyl, c-hexyl, c-heptyl, c-octyl, 1-methyl-c-hexyl, 2-methyl-c-hexyl, 3-methyl-c-hexyl, ~~1,2-dimethyl-c-hexyl~~ 1,2-dimethyl-c-hexyl, ~~2,3-dimethyl-c-propyl~~, ~~1-ethyl-c-propyl~~, 1-methyl-c-pentyl, 2-methyl-c-pentyl, 3-methyl-c-pentyl, 1-ethyl-c-butyl, 2-ethyl-c-butyl, 3-ethyl-c-butyl, 1,2-dimethyl-c-butyl, 1,3-dimethyl-c-butyl, 2,2-dimethyl-c-butyl, 2,3-dimethyl-c-butyl, 2,4-dimethyl-c-butyl, 3,3-dimethyl-c-butyl, 1-n-propyl-c-propyl, 2-n-propyl-c-propyl, 1-i-propyl-c-propyl, 2-i-propyl-c-propyl, 1,2,2-trimethyl-c-propyl, 1,2,3-trimethyl-c-propyl, 2,2,3-trimethyl-c-propyl, 1-ethyl-2-methyl-c-propyl, 2-ethyl-1-methyl-c-propyl, 2-ethyl-2-methyl-c-propyl, 2-ethyl-3-methyl-c-propyl, and the like.



Please replace the paragraph beginning on page 24, line 7 with the following paragraph:

Examples of C<sub>3-8</sub> cycloalkenyl group are such as 1-c-pentenyl, 2-c-pentenyl, 3-c-pentenyl, 1-methyl-2-c-pentenyl, 1-methyl-3-c-pentenyl, 2-methyl-1-c-pentenyl, 2-methyl-2-c-pentenyl, 2-methyl-3-c-pentenyl, 2-methyl-4-c-pentenyl, ~~2-methyl-5-c-pentenyl~~, 2-methylene-c-pentyl, 3-methyl-1-c-pentenyl, 3-methyl-2-c-pentenyl, 3-methyl-3-c-pentenyl, 3-methyl-4-c-pentenyl, ~~3-methyl-5-c-pentenyl~~, 3-methylene-c-pentyl, 1-c-hexenyl, 2-c-hexenyl, 3-c-hexenyl, ~~4-c-heptynyl~~, ~~2-c-heptynyl~~, ~~3-c-heptynyl~~, ~~4-c-heptynyl~~, ~~1-c-octynyl~~, ~~2-c-octynyl~~, ~~3-c-octynyl~~, ~~4-c-octynyl~~, 2-c-heptenynyl, 3-c-heptenynyl, 4-c-heptenynyl, 1-c-octenynyl, 2-c-octenynyl, 3-c-octenynyl, 4-c-octenynyl, and the like.

Please replace the paragraph starting on page 29, line 1 with the following paragraph:

Examples of di-C<sub>1-6</sub> alkylaminocarbonyl group are such as dimethylaminocarbonyl, diethylaminocarbonyl, di-n-propylaminocarbonyl, di-i-propylaminocarbonyl, di-c-propylaminocarbonyl, di-n-butylaminocarbonyl, di-i-butylaminocarbonyl, di-s-butylaminocarbonyl, di-t-butylaminocarbonyl, di-c-butylaminocarbonyl, di-1-pentylaminocarbonyl, di-2-pentylaminocarbonyl, di-3-pentylaminocarbonyl, di-i-pentylaminocarbonyl, di-neopentylaminocarbonyl, di-t-pentylaminocarbonyl, di-c-pentylaminocarbonyl, di-1-hexylaminocarbonyl, di-2-hexylaminocarbonyl, di-3-hexylaminocarbonyl, di-c-hexylaminocarbonyl, di-(1-methyl-n-pentyl)aminocarbonyl, di-(1,1,2-trimethyl-n-propyl)aminocarbonyl, di-(1,2,2-trimethyl-n-propyl)aminocarbonyl, di-(3,3-dimethyl-n-butyl)aminocarbonyl, methyl(ethyl)aminocarbonyl, methyl(n-propyl)aminocarbonyl, methyl(i-propyl)aminocarbonyl, methyl(c-propyl)aminocarbonyl, methyl(n-butyl)aminocarbonyl, methyl(i-butyl)aminocarbonyl,

methyl(s-butyl)aminocarbonyl, methyl(t-butyl)aminocarbonyl,  
 methyl(c-butyl)aminocarbonyl, ethyl(n-propyl)aminocarbonyl, ethyl(i-propyl)aminocarbonyl,  
 ethyl(c-propyl)aminocarbonyl, ethyl(n-butyl)aminocarbonyl, ethyl(i-butyl)aminocarbonyl,  
 ethyl(s-butyl)aminocarbonyl, ethyl(t-butyl)aminocarbonyl, ethyl(c-butyl)aminocarbonyl,  
 n-propyl(i-propyl)aminocarbonyl, n-propyl(c-propyl)aminocarbonyl,  
 n-propyl(n-butyl)aminocarbonyl, n-propyl(i-butyl)aminocarbonyl, n-  
 propyl(s-butyl)aminocarbonyl, n-propyl(t-butyl)aminocarbonyl,  
 n-propyl(c-butyl)aminocarbonyl, ~~i-propyl(c-butyl)aminocarbonyl~~ i-propyl(c-  
propyl)aminocarbonyl, i-propyl(n-butyl)aminocarbonyl, i-propyl(i-butyl)aminocarbonyl,  
 i-propyl(s-butyl)aminocarbonyl, i-propyl(t-butyl)aminocarbonyl,  
 i-propyl(c-butyl)aminocarbonyl, c-propyl(n-butyl)aminocarbonyl,  
 c-propyl(i-butyl)aminocarbonyl, c-propyl(s-butyl)aminocarbonyl,  
 c-propyl(t-butyl)aminocarbonyl, c-propyl(c-butyl)aminocarbonyl, n-butyl(i-  
 butyl)aminocarbonyl, n-butyl(s-butyl)aminocarbonyl, n-butyl(t-butyl)aminocarbonyl,  
 n-butyl(c-butyl)aminocarbonyl, i-butyl(s-butyl)aminocarbonyl, i-butyl(t-butyl)aminocarbonyl,  
~~i-butyl(t-butyl)aminocarbonyl~~, i-butyl(c-butyl)aminocarbonyl,  
 s-butyl(t-butyl)aminocarbonyl, s-butyl(c-butyl)aminocarbonyl,  
 t-butyl(c-butyl)aminocarbonyl, and the like.

Please replace the paragraph beginning on page 30, line 8 with the following paragraph:

Examples of C<sub>3-8</sub> cycloalkylcarbonyl group are such as c-propylcarbonyl,  
 c-butylcarbonyl, i-methyl-c-propylcarbonyl, 2-methyl-c-propylcarbonyl,  
 c-pentylcarbonyl, 1-methyl-c-butylcarbonyl, 2-methyl-c-butylcarbonyl,  
 3-methyl-c-butylcarbonyl, 1,2-dimethyl-c-propylcarbonyl,

2,3-dimethyl-c-propylcarbonyl, 1-ethyl-c-propylcarbonyl, 2-ethyl-c-propylcarbonyl, c-hexylcarbonyl, c-heptylcarbonyl, c-octylcarbonyl, 1-methyl-c-hexylcarbonyl, 2-methyl-c-hexylcarbonyl, 3-methyl-c-hexylcarbonyl, ~~1,2-dimethyl-c-hexylcarbonyl~~, 1,2-dimethyl-c-hexylcarbonyl, 2,3-dimethyl-c-propylcarbonyl, 1-ethyl-c-propylcarbonyl, 1-methyl-c-pentylcarbonyl, 2-methyl-c-pentylcarbonyl, 3-methyl-c-pentylcarbonyl, 1-ethyl-c-butylcarbonyl, 2-ethyl-c-butylcarbonyl, 3-ethyl-c-butylcarbonyl, 1,2-dimethyl-c-butylcarbonyl, 1,3-dimethyl-c-butylcarbonyl, 2,2-dimethyl-c-butylcarbonyl, 2,3-dimethyl-c-butylcarbonyl, 2,4-dimethyl-c-butylcarbonyl, 3,3-dimethyl-c-butylcarbonyl, 1-n-propyl-c-propylcarbonyl, 2-n-propyl-c-propylcarbonyl, 1-i-propyl-c-propylcarbonyl, 2-i-propyl-c-propylcarbonyl, 1,2,2-trimethyl-c-propylcarbonyl, 1,2,3-trimethyl-c-propylcarbonyl, 2,2,3-trimethyl-c-propylcarbonyl, 1-ethyl-2-methyl-c-propylcarbonyl, 2-ethyl-1-methyl-c-propylcarbonyl, 2-ethyl-2-methyl-c-propylcarbonyl, 2-ethyl-3-methyl-c-propylcarbonyl, and the like.

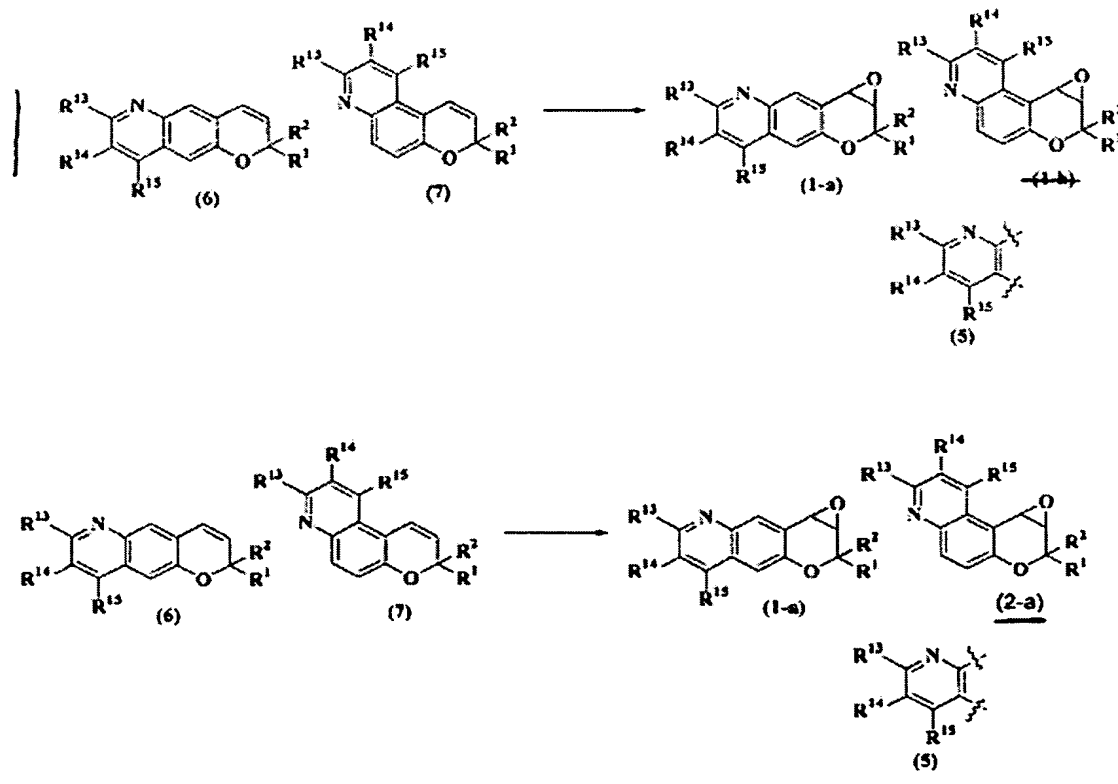
Please replace the paragraph beginning on page 47, line 14 with the following paragraph:

(5) The benzopyran derivative or pharmaceutically acceptable salt thereof as set forth in (3), wherein  $R^6$  is alkyl group, cycloalkyl group or ~~cycloalkenyl~~ cycloalkenyl ring;

Please replace the paragraph beginning on page 305, line 25 with the following paragraph:

The compound of formulae (1-a) or (2-a) that is the compound of formula (I) or (II) wherein A is the group of formula (5),  $R^4$  is hydrogen atom and  $R^3$  is hydroxy group can be

obtained from the compound of formula (6) or (7) according to known methods (methods described in J. M. Evans et al., J. Med. Chem. 1984, 27, 1127; J. Med. Chem. 1986, 29, 2194; J. T. North et al., J. Org. Chem. 1995, 60, 3397; as well as Japanese Patent Laid-open Nos. Sho 56-57785, Sho 56-57786, Sho 58-188880, Hei 2-141, Hei 10-87650 and Hei 11-209366 and the like).



Please replace the paragraph beginning on page 307, line 1 with the following paragraph:

The transition metal catalysts used include ruthenium chloride, dichlorotris(triphenylphosphine)ruthenium, dibromotris(triphenylphosphine)ruthenium, dihydridetetrakis(triphenylphosphine)ruthenium, ( $\eta$ 4-cyclooctadiene)( $\eta$ 6-cyclooctatriene)ruthenium, dichlorotricarbonyl ruthenium dimer, dodecacarbonyl triruthenium, ( $\eta$ 5-pentamethylcyclopentadienyl)chloro( $\eta$ 4-cyclooctatriene)ruthenium( $\eta$ 5-

pentamethylcyclopentadienyl)chloro( $\eta$ 4-cyclooctadiene)ruthenium, palladium acetate, palladium chloride, dichlorobis(triphenylphosphine)palladium, tetrakis(triphenylphosphine) palladium, bis(dibenzylideneacetone)palladium, rhodium chloride, chlorotris(triphenylphosphine)rhodium, hydridecarbonyltristriphenylphosphine rhodium, hydridetris(triphenylphosphine)rhodium, di- $\eta$ -chlorotetracarbonyl dirhodium, chlorocarbonylbis(triphenylphosphine)iridium, ( $\eta$ 5-pentamethylcyclopentadienyl)dichloroiridium dimer, nickeltetrakis(triphenylphosphine), dicobaltoctacarbonyl, ( $\eta$ 5-cyclopentadienyl)dicarbonylcobalt, and the like.

Please replace the paragraph bridging pages 315 and 316 with the following paragraph:

To a solution of 6-amino-2,2-dimethylchromene (10.1 g, 57.7 mmol) in ethanol (500 mL), methylvinylketone (33.0 mL, 404 mmol), m-nitrobenzenesulfonic acid (21.1 g, 104 mmol), zinc chloride (1.97 g, 14.4 ~~mol~~ mmol) and 35% hydrochloric acid (24 mL, 289 mmol) were added at room temperature and the resulting mixture was stirred at 110°C for 5 hours. Upon the completion of the reaction, ethanol was distilled off, water was added, and the resulting solution was neutralized with sodium hydrogencarbonate and extracted with ethyl acetate. The resulting organic phase was washed with sodium chloride aqueous solution, and dried over anhydrous magnesium sulfate. After distilling off the solvent, the residue was purified by medium pressure column chromatography (hexane/ethyl acetate = 3/1) and the aimed product was obtained (yield: 38%).

Please replace the paragraph beginning on page 316, line 8 with the following paragraph:

Brown amorphous product

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.51(s, 6H), 2.59(d,  $J = 0.6$  Hz, 3H), 5.90(d,  $J = 9.9$  Hz, 1H), ~~6.59(d,  $J = 9.9$  Hz, 1H)~~ 6.59(d,  $J = 9.9$  Hz, 1H), 7.11(d,  $J = 3.6$  Hz, 1H), 7.25(s, 1H), 7.68(s, 1H), 8.57(d,  $J = 4.4$  Hz, 1H)

MS( $\text{ESI}^+$ ) $m/z$ ; 226  $[\text{M}+1]^+$

Please replace the paragraph beginning on page 318, line 6 with the following paragraph:

(Yield: 59%)

Black brown oily product

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.49(s, 6H), 2.54(s, 3H), 2.62(s, 3H), 5.86(d,  $J = 9.9$  Hz, 1H), ~~6.55(d,  $J = 9.9$  Hz, 1H)~~ 6.55(d,  $J = 9.9$  Hz, 1H), 7.00(s, 1H), 7.20(s, 1H), 7.60(s, 1H)

MS( $\text{ESI}^+$ ) $m/z$ ; 240 $[\text{M}+1]^+$

Please replace the paragraph beginning on page 319, line 11 with the following paragraph:

(Yield: 50%)

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.50(s, 6H), 2.50(s, 3H), 2.66(s, 3H), 5.87(d,  $J = 9.9$  Hz, 1H), ~~6.57(d,  $J = 9.9$  Hz, 1H)~~ 6.57(d,  $J = 9.9$  Hz, 1H), 7.26(s, 1H), 7.63(s, 1H), 8.48(s, 1H)

MS( $\text{ESI}^+$ ) $m/z$ ; 240  $[\text{M}+1]^+$

Please replace the paragraph beginning on page 326, line 8 with the following paragraph:

Pale yellow solid

mp: 65-67°C

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.86(s, 6H), 2.70(s, 1H), 7.69-7.71(2H), 7.80(s, 1H), 8.33(d,  $J = 8.3$  Hz, 1H), 8.45(d,  $J = 8.3$  Hz 1H), 9.01(br s, 1H)

~~MS(GC)m/z~~ MS(EI)m/z; 211  $[\text{M}]^+$

Please replace the paragraph beginning on page 326, line 20 with the following paragraph:

Green crystal

mp: 104-107°C

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.54(s, 6H), 5.89(d,  $J = 10.2$  Hz, 1H), 6.93(d,  $J = 10.2$  Hz, 1H), 7.50(d,  $J = 9.1$  Hz, 1H), 7.73(br s, 1H), 8.31(d,  $J = 9.1$  Hz, 1H), 8.74(d,  $J = 8.5$  Hz, 1H), 9.03(br s, 1H)

~~MS(GC)m/z~~ MS(EI)m/z; 211 $[\text{M}]^+$

Please replace the paragraph beginning on page 339, line 2 with the following paragraph:

(Yield: 78%)

~~97.1%-99.1%ee~~; CHIRALCEL OJ-R acetonitril/methanol/0.01 M sodium chloride aqueous solution = 1/3/3, Retention time: 18.9 min.

Yellow amorphous product

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.28(s, 3H), 1.65(s, 3H), 2.59(d,  $J = 0.8$  Hz, 3H), 3.60(d,  $J = 4.4$  Hz, 1H), 4.13(d,  $J = 4.4$  Hz, 1H), 7.19(s, 1H), 7.29(d, 1H), 8.02(s, 1H)

MS( $\text{ESI}^+$ )m/z; 276  $[\text{M}+1]^+$

Please replace the paragraph beginning on page 345, line 18 with the following paragraph:

Synthesis Example 26

~~(3*R*\*,4*S*\*) 4-[[2-(4-aminophenyl)ethyl]amino]-2,2,9-trimethyl-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinolin-3-ol~~ (3*R*\*,4*S*\*)-4-[[2-(4-aminophenyl)ethyl]amino]-7-chloro-2,2,9-trimethyl-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinolin-3-ol

(Yield: 40%)

Colorless amorphous product

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.23 (s, 3H), 1.55 (s, 3H), 1.58 (br s, 3H), 2.57 (s, 3H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.85-3.05 (m, 2H), 3.11 (br s, 1H), 3.57 (d, *J* = 10.4 Hz, 1H), 3.84 (d, *J* = 10.4 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 7.11 (s, 1H), 7.25 (s, 1H), 7.81 (s, 1H).

MS (ESI<sup>+</sup>) *m/z*; 412 [M+1]<sup>+</sup>

MS (ESI<sup>+</sup>) *m/z*; 456 [M+45]<sup>+</sup>

Please replace the paragraph bridging pages 346 and 347 with the following paragraph:

Synthesis Example 30

~~(3*R*\*,4*S*\*)-7-chloro-2,2,9-trimethyl-4-[[2-(1-piperidiny)ethyl]amino]-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinolin-3-ol~~

(Yield: 61%)

Pale yellow amorphous product

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.29 (s, 3H), 1.58 (s, 3H), 1.60 (br s, 2H), 1.50-1.70 (m, 6H), 2.30-2.60 (m, 6H), ~~2.58 (s, 3H), 3.06 (t, *J* = 5.8 Hz, 2H)~~ 2.58 (s, 3H), 3.06 (t, *J* = 5.8 Hz, 2H), 3.54 (d, *J* = 10.4 Hz, 1H), 3.80 (d, *J* = 10.4 Hz, 1H), 7.13 (s, 1H), 7.23 (s, 1H), 8.06 (s, 1H).



MS (ESI<sup>+</sup>) m / z; 404 [M+1]<sup>+</sup>

MS (ESI<sup>-</sup>) m / z; 448 [M+45]<sup>+</sup>

Please replace the paragraph bridging pages 348-349 with the following paragraph:

Synthesis Example 35

(3*R*\*,4*S*\*)-7-chloro-2,2,9-trimethyl-4-[(2,2-diethoxyethyl)amino]-3,4-dihydro-2*H*-pyrano[2,3-  
g]quinolin-3-ol ~~maleate~~ 1-maleate

(Yield: 88%)

White solid

<sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 1.23-1.30 (m, 9H), 1.57 (s, 3H), 2.64 (s, 3H), 3.50-3.85 (m, 4H), 4.02  
(d, *J* = 10.2 Hz, 1H), 6.27 (s, 1H), 7.37 (s, 1H), 7.49 (s, 1H), 8.13 (s, 1H)

Free form

(3*R*\*,4*S*\*)-7-chloro-2,2,9-trimethyl-4-[(2,2-diethoxyethyl)amino]-3,4-dihydro-2*H*-pyrano[2,3-  
g]quinolin-3-ol

Pale yellow amorphous product

MS (ESI<sup>+</sup>) m / z; 410 [M+1]<sup>+</sup>

MS (ESI<sup>-</sup>) m / z; 453 [M+45]<sup>+</sup>

Please replace the paragraph beginning on page 350 with the following paragraph:

Synthesis Example 40

~~(3*R*\*,4*S*\*)-7-chloro-2,2,9-trimethyl-4-[[2-(2-pyridyl)ethyl]amino]-3,4-dihydro-2*H*-  
pyrano[2,3-g]quinolin-3-ol~~ (3*R*\*,4*S*\*)-7-chloro-2,2,9-trimethyl-4-[[2-(2-pyridyl)ethyl]amino]-  
3,4-dihydro-2*H*-pyrano[2,3-g]quinolin-3-ol

(Yield: 83%)

Yellow amorphous product

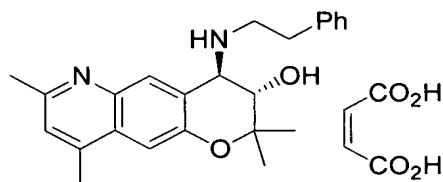
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.32 (s, 3H), 1.61 (s, 3H), 1.82 (br), 2.57 (s, 3H), 2.92-3.12 (m, 2H), 3.26-3.30 (m, 2H), 3.74 (d,  $J = 10.2$  Hz, 1H), 3.92 (d,  $J = 10.2$  Hz, 1H), 7.13 (s, 1H), 7.17-7.27 (m, 3H), 7.64-7.70 (m, 1H), 8.06 (s, 1H), 8.56 (d,  $J = 5.0$  Hz, 1H)

MS ( $\text{ESI}^+$ )  $m/z$ ; 398  $[\text{M}+1]^+$

Please replace the paragraph bridging pages 354 and 355 with the following paragraph:

#### Synthesis Example 51

~~(3*R*\*,4*R*\*) 2,2,7,9-tetramethyl-4-[(2-pentylethyl)amino]-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinolin-3-ol 1 maleate (3*R*\*,4*R*\*)-2,2,7,9-tetramethyl-4-[(2-phenethyl)amino]-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinolin-3-ol 1 maleate~~



This compound was synthesized according to the process of Synthesis Example 50.

(2-step yield: 25%)

~~epoxy-epoxide~~ 99.1% ee CHIRALPAK AD-RH 20 mM phosphate buffer (pH 8.0)/acetonitrile = 60/40, Retention time: 10.3 min.

White crystal

mp: 215-216°C (decomposition)

$^1\text{H-NMR}$ ( $\text{DMSO-d}_6$ ); 1.16(s, 3H), 1.49(s, 3H), 2.55(s, 3H), 2.58(s, 3H), 2.97-3.32 (m, 4H), 4.02-4.04(m, 1H), 4.62(br s, 1H), 6.04(s, 2H), 6.25(br s, 1H), 7.24-7.36(m, 7H), 8.31(s, 1H)

MS( $\text{ESI}^+$ ) $m/z$ ; 377  $[\text{M}+1]^+$

Please replace the paragraph bridging pages 358 and 259 with the following paragraph:

#### Synthesis Example 55

~~(3*R*\*,4*S*\*)-7-chloro-2,2,9-trimethyl-4-[(2-tetrahydro-2*H*-thiopyran-4-ylethyl)amino]-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinolin-3-ol~~ (3*R*\*,4*S*\*)-7-chloro-2,2,9-trimethyl-4-{[2-tetrahydro-2*H*-thiopyran-4-ylethyl]amino}-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinolin-3-ol

(Yield: 63%)

Colorless amorphous product

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.28 (s, 3H), 1.40-1.60 (m, 5H), 1.56 (s, 1H), 1.90-2.00 (m, 2H), 2.59 (s, 3H), 2.50-2.85 (m, 6H), 3.23 (s, 1H), 3.63 (d, *J* = 10.4 Hz, 1H), 3.87 (d, *J* = 10.4 Hz, 1H), 7.16 (s, 1H), 7.28 (s, 1H), 7.91 (s, 1H).

MS (ESI<sup>+</sup>) *m/z*; 421 [M+1]<sup>+</sup>

MS (ESI<sup>-</sup>) *m/z*; 465 [M+45]<sup>+</sup>

Please replace the paragraph beginning after page 361, line 1 with the following paragraph:

Under hydrogen stream at 1 atm, a solution of (3*R*\*,4*S*\*)-6-amino-3,4-dihydro-2,2-dimethyl-7-nitro-4-(2'-phenylethylamino)-2*H*-benzopyran-3-ol (10.0 g, 28.0 mmol) and 5% palladium carbon (AER type, 1 g) in ethanol (200 mL) was stirred at room temperature for 6 hours. Upon the completion of the reaction, the reaction solution was filtered through celite and concentrated to obtain the aimed product (yield: 98%).

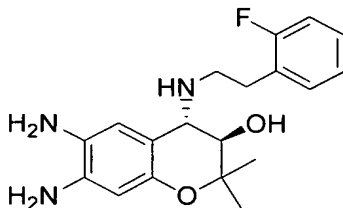
Black amorphous product

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.13 (s, 3H), 1.43 (s, 3H), ~~2.60-3.0~~ 2.60-3.00 (m, 4H), 2.5-3.5 (br 6H), 3.47 (d, *J* = 9.6 Hz, 1H), 3.51 (d, *J* = 9.6 Hz, 1H), 6.12 (s, 1H), 6.14 (s, 1H), 7.15-7.50 (m, 5H)

MS (ESI)  $m/z$ ; 400[M+1]<sup>+</sup>, 327 (bp).

Please replace the paragraph beginning on page 362, line 18 with the following paragraph:

~~(3*R*\*,4*S*\*)-6,7-diamino-4-[[2-(2-fluorophenyl)ethyl]amino]-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-3-ol~~  
(3*R*\*,4*S*\*)-6,7-diamino-4-[[2-(2-fluorophenyl)ethyl]amino]-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-3-ol



(Yield: 87%)

Black amorphous product

MS (ESI<sup>+</sup>)  $m/z$ ; 346 [M+1]<sup>+</sup>

MS (ESI<sup>-</sup>)  $m/z$ ; 380 [M+45]<sup>+</sup>

Please replace the paragraph beginning on page 364, line 2 with the following paragraph:

~~(8*R*\*,9*S*\*)-[[2-(4-fluorophenyl)ethyl]amino]-7,7-dimethyl-8,9-dihydro-7*H*-pyrano[2,3-*g*]quinoxalin-8-ol hydrochloride~~  
(3*R*\*,4*S*\*)-[[2-(4-fluorophenyl)ethyl]amino]-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinoxalin-3-ol hydrochloride

(Yield: 95%)

Brown crystal

mp: 191-197°C (decomposition)

Please replace the paragraph beginning on page 365, line 17 with the following paragraph:

(3*R*\*,4*S*\*)-4-[(2-hydroxy-2-phenylethyl)amino]-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinoxalin-3-ol  
(Yield: 66%)

Two diastereomers that can not be ~~divided~~ separated

Gray amorphous product

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.30 (s, 3H), 1.58 (s, 1.5H), 1.59 (s, 1.5H), 1.70 (br s, 3H), 2.90-3.10 (m, 2H), 3.71 (d, *J* = 10.5Hz, 1H), 3.95-4.05 (m, 1H), 7.20-7.45 (m, 6H), 8.10 (s, 0.5H), 8.12 (s, 0.5H), 8.64 (d, *J* = 1.9 Hz, 1H), 8.73 (d, *J* = 1.9 Hz, 1H).

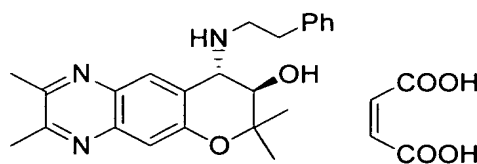
MS (ESI<sup>+</sup>) *m/z*; 366 [M+1]<sup>+</sup>

MS (ESI<sup>-</sup>) *m/z*; 410 [M+45]<sup>+</sup>

Please replace the paragraph beginning on page 367, line 5 with the following paragraph:

#### Synthesis Example 64

~~(3*R*\*,4*S*\*)-2,2,7,8-tetramethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinoxalin-3-ol maleate~~ (3*R*\*,4*S*\*)-2,2,7,8-tetramethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinoxalin-3-ol 1-maleate



Synthesis Example 64 was carried out similarly to the process of Synthesis Example 59.

Please replace the paragraph beginning on page 369, line 23 (last line) with the following paragraph:

(3*R*\*4*S*\*)-2,2,8-trimethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinoxalin-3-ol 1-maleate

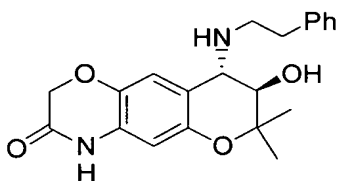
Please replace the paragraph beginning on page 372, line 2 with the following paragraph:

To a solution of (±)-trans-6,7-diamino-3,4-dihydro-2,2-dimethyl-4-(2'-phenylethylamino)-2*H*-1-benzopyran-3-ol (500 mg, 1.53 mmol) in dioxane (7 mL), 4 mol/L hydrochloric acid/dioxane solution (0.38 mL) was added, and the resulting mixture was stirred at room temperature for 15 minutes. Then, phenyl chloroformate (0.21 mL, 1.53 mmol) and triethylamine (0.21 mL, 1.53 mmol) were added thereto, and the resulting mixture was stirred at room temperature for 1 hour. Further, triethylamine (0.63 mL, 4.58 mmol) was added thereto, and the resulting mixture was stirred at room temperature for 2 hours. Upon the completion of the reaction, 1 mol/L hydrochloric acid was added thereto and thereby adjusted to pH 7-8. Thereafter, the resulting reaction solution was extracted with ethyl acetate, washed with saturated sodium chloride aqueous solution, and then dried over sodium sulfate and concentrated. The resulting mixture was purified by silica gel column (methanol/chloroform = 1/20) to obtain the aimed product (~~yield: 40%~~) (yield: 4%).

Please replace the paragraph beginning on page 372, line 20 with the following paragraph:

#### Synthesis Example 71

(7*R*\*,8*S*\*)-7-hydroxy-6,6-dimethyl-8-(2-phenylethyl)amino]-4,6,7,8-tetrahydro-1,5-dioxo-4-aza-anthracene-3-one



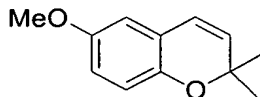
~~4-(1,1-dimethyl-2-propenyloxy)anisole~~ 4-(1,1-dimethyl-2-propynyloxy)anisole

Please replace the paragraph at the beginning of page 373 with the following paragraph:

To a solution of 4-methoxyphenol (15.0 g, 121 mmol) in acetonitrile (75 mL), 1,8-diazabicyclo[5.4.0]undecene (23.9 g, 157 mmol) was added under ice cooling and the resulting mixture was stirred at 0°C for 30 minutes (Solution 1). To a solution of ~~2-methyl-3-buten-2-ol~~ 2-methyl-3-butyn-2-ol (11.7 g, 139 mmol) in acetonitrile (75 mL), 1,8-diazabicyclo[5.4.0]undecene (23.9 g, 157 mmol) was added under ice cooling, the resulting mixture was stirred at 0°C for 30 minutes, then trifluoroacetic anhydride (25.4 g, 121 mmol) was added and the resulting mixture was stirred at 0°C for 30 minutes (Solution 2). Copper (I) chloride (36 mg, 0.36 mmol) was added to Solution 1, and then Solution 2 was added dropwise thereto over 15 minutes. Upon the ~~completion~~ completion of dropwise addition, the temperature was raised to room temperature, and the mixture was stirred overnight. Upon the completion of the reaction, an aqueous solution of ammonium chloride was added to the reaction solution, and the solvent was distilled off under a reduced pressure. An aqueous solution of 1 mol/L hydrochloric acid was added to the residue, the resulting mixture was extracted with ethyl acetate, the organic phase was washed once with an aqueous solution of 1 mol/L hydrochloric acid, twice with an aqueous solution of saturated sodium hydrogen carbonate and once with saturated sodium chloride solution. Then, the organic phase was dried over anhydrous magnesium sulfate. After distilling off the solvent, the residue was directly used for the subsequent reaction.

Please replace the paragraph beginning after page 373, line 19 with the following paragraph:

6-methoxy-2,2-dimethyl-2H-1-benzopyran



A solution of ~~4-(1,1-dimethyl-2-propenyloxy)anisole~~ 4-(1,1-dimethyl-2-propynyloxy)anisole in 1,2-dichlorobenzene (50 mL) was stirred at 190°C for 2 hours. Upon the completion of the reaction, the solvent was distilled off under a reduced pressure. The residue was purified by column chromatography (hexane/chloroform = 3/1) and the aimed product was obtained as red oily substance (2-step, yield: 61%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.41 (s, 6H), 3.75 (s, 3H), 5.64 (d, *J*=9.9 Hz, 1H), 6.28 (d, *J*=9.9 Hz, 1H), 6.55 (d, *J*=2.7 Hz, 1H), 6.64-6.73 (m, 2H)

LC/MS (ESI<sup>+</sup>)m/z: 191[M<sup>+</sup>+1]

Please replace the paragraph beginning after page 374, line 2 with the following paragraph:

A mixed solution of acetic acid (6.2 mL) and acetic anhydride (6.2 mL) containing 6-methoxy-2,2-dimethyl-2H-1-benzopyran (3.1 g, 16.4 mmol) was cooled with ice, nitric acid (1.37 mL, 18.0 mmol) was added dropwise and then the mixture was stirred at 0°C for 1 hour. Upon the completion of the reaction, an aqueous solution of 1 mol/L sodium hydroxide was added to the reaction solution, the resulting solution was extracted with ethyl acetate (150 mL). The organic phase was washed twice with 1 mol/L sodium hydroxide aqueous solution and once with saturated sodium chloride solution. Then, the organic phase was dried over anhydrous magnesium sulfate. After distilling off the solvent, the residue was purified by



column chromatography (hexane/ethyl acetate = 6/1) and the aimed product was obtained as yellow crystal (yield: 79%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.44 (s, 6H), 3.91 (s, 3H), 5.85 (d,  $J=9.6$  Hz, 1H), 6.33 (d,  $J=9.6$  Hz, 1H), 6.69 (s, 1H), 7.34 (s, 1H)

~~LC/MS (ESI $^+$ ): 236 [ $\text{M}^+ + 1$ ]~~ LC/MS (ESI $^+$ )m/z: 236 [ $\text{M}^+ + 1$ ]

Please replace the paragraph bridging pages 374 and 375 with the following paragraph:

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.26 (s, 3H), 1.58 (s, 3H), 3.53 (d,  $J=4.3$  Hz, 1H), 3.90 (d,  $J=4.3$  Hz, 1H), 3.95 (s, 3H), 7.08 (s, 1H), 7.33 (s, 1H)

~~MS (EI): 251 [ $\text{M}^+$ ]~~ MS (EI)m/z: 251 [ $\text{M}^+$ ]

HPLC: 18.6 min (enantiomer 24.1 min)

HPLC condition: chiralcel OJ-RH, MeCN/MeOH/0.01 M NaCl aq. = 1/3/5, 1.0 ml/min, 40°C, 256 nm

Please replace the paragraph beginning on page 375, line 9 with the following paragraph:

To a solution of (3*R*\*, 4*S*\*)-3,4-epoxy-6-methoxy-2, 2-dimethyl-7-nitro-3,4-dihydro-2H-1-benzopyran (2.50 g, 9.95 mmol) in 1,4-dioxane (5.0 mL), lithium perchlorate (1.06 g, 9.95 mmol) and 4-(phenylethyl)amine (1.50 mL, 11.9 mmol) were added at room temperature and the mixture was stirred at 80 °C for 1 hour. Upon the completion of the reaction, an aqueous solution of saturated ammonium chloride was added to the reaction solution, and the resulting solution was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. After distilling off the solvent, the residue was purified by column chromatography (hexane/ethyl

acetate = 6/4) and the aimed product was obtained as orange amorphous substance (quantitative yield).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.15 (s, 3H), 1.47 (s, 3H), 2.73-2.95 (m, 4H), 3.60 (d,  $J=10.0$  Hz, 1H), 3.68 (d,  $J=10.0$  Hz, 1H), 3.73 (s, 3H), 6.78 (s, 1H), 7.21-7.35 (m, 6H)

$\text{MS (EI): } 372[\text{M}^+]$   $\text{MS (EI)m/z: } 372[\text{M}^+]$

Please replace the paragraph bridging pages 375 and 376 with the following paragraph:

To a solution of (3*R*\*, 4*S*\*)-6-methoxy-2, 2-dimethyl-7-nitro-4-[(2-phenylethyl)amino]-3,4-dihydro-2H-1-benzopyran-3-ol (407 mg, 1.09 mmol) and di-*t*-butyl carbonate (477 mg, 2.19 mmol) in tetrahydrofuran (6.0 mL), triethylamine (305 mL, 2.19 mmol) was added at 0 °C and the mixture was stirred at room temperature overnight. Upon the completion of the reaction, an aqueous solution of saturated sodium carbonate was added to the reaction solution, and the resulting solution was extracted with ethyl acetate. The organic phase was washed with 1 mol/L hydrochloric acid aqueous solution and saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. After distilling off the solvent, the residue was purified by column chromatography (hexane/ethyl acetate = 4/1) and the aimed product was obtained as yellow amorphous substance (yield: 88%).

$\text{MS (EI): } 473[\text{M}^++1]$   $\text{MS (EI)m/z: } 473[\text{M}^++1]$

Please replace the paragraph beginning on page 376, line 15 with the following paragraph:

A solution of *t*-butyl (2-phenylethyl) (3*R*\*, 4*S*\*)-3-hydroxy-6-methoxy-2, 2-dimethyl-7-nitro-3,4-dihydro-2H-1-benzopyran-4-yl carbamate (1.32 g, 2.80 mmol) and 5% palladium-carbon (132 mg) in methanol (26 mL) was stirred under hydrogen atmosphere at room

temperature overnight. Upon the completion of the reaction, the reaction solution was filtered through celite. After distilling off the solvent, the residue was purified by column chromatography (hexane/ethyl acetate = 4/1) and the aimed product was obtained (yield: 94%).

Colorless solid

~~LC/MS (ESI<sup>+</sup>): 443[M<sup>+</sup>+1]~~ LC/MS (ESI<sup>+</sup>)m/z: 443[M<sup>+</sup>+1]

Please replace the paragraph bridging pages 377 and 378 with the following paragraph:

To a solution of t-butyl (2-phenylethyl) (3*R*\*, 4*S*\*)-[7-(2-chloro-acetamide)-3-hydroxy-6-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl carbamate (251 mg, 0.48 mmol) in methylene chloride (5 mL), borane ~~trichloride~~ tribromide (1M solution in methylene chloride, 2.42 mL, 2.42 mmol) was added at 0 °C, and the resulting mixture was stirred for 2 hours. Upon the completion of the reaction, water was added thereto, the resulting solution was extracted with ethyl acetate, washed with saturated sodium hydrogencarbonate aqueous solution and then with saturated sodium chloride solution, dried over magnesium sulfate, and concentrated. The resulting mixture was purified by silica gel column (hexane/ethyl acetate = 2/1) and the aimed product was obtained (yield: 70%).

Pale pink amorphous product

Please replace the paragraph bridging pages 381 and 382 with the following paragraph:

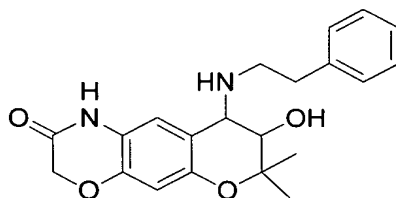
To a solution of (7*R*\*, 8*S*\*)-7-hydroxy-4,6,6-trimethyl-8-(2-phenylethyl)amino]-4,6,7,8-tetrahydro-1,5-dioxo-4-aza-anthracene-3-one (65 mg, 0.17 mmol) in ether (2.2 mL), 4 mol/L hydrogen ~~chloride-ethene~~ chloride-dioxane (200 µL) was added at room temperature,

and the resulting mixture was stirred at room temperature for 10 minutes. Upon the completion of the reaction, the resulting crystal was filtered off and the aimed product was obtained (yield: 93%).

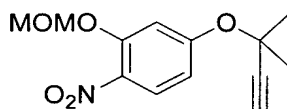
Please replace the paragraph beginning on page 382, line 6 with the following paragraph:

#### Synthesis Example 74

7-Hydroxy-6,6-dimethyl-8-(2-phenylethylamino)-7,8-dihydro-1H,6H-4,5-dioxo-1-aza-anthracene-2-one



~~2-methoxymethoxy-4-(1,1-dimethyl-2-propionyloxy)-1-nitro-benzene~~  
2-methoxymethoxy-4-(1,1-dimethyl-2-propynyloxy)-1-nitro-benzene



Please replace the paragraph beginning on page 383, line 3 with the following paragraph:

A solution of ~~2-methoxymethoxy-4-(1,1-dimethyl-2-propionyloxy)-1-nitro-benzene~~  
2-methoxymethoxy-4-(1,1-dimethyl-2-propynyloxy)-1-nitro-benzene (2.1 g, 7.92 mmol) in ~~dichlorobenzene~~  
1,2-dichlorobenzene (21 mL) was stirred at 20°C for 0.5 hour. Upon the completion of the reaction, the resulting mixture was concentrated and purified by silica gel column (hexane/ethyl acetate = 5/1). Thereby, a mixture (1:1) of the aimed product and the

~~positional isomer~~ regioisomer was obtained (yield: 77%).

Yellow oily product

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.46 (s, 6H), 3.53 (s, 1.5 H), 3.58 (s, 1.5H), 5.10 (s, 1H), 5.27 (s, 1H), 5.64 (d, J = 10.4 Hz, 0.5H), 5.74 (d, J = 10.4 Hz, 0.5H), 6.27 (d, J = 10.4 Hz, 0.5H), 6.60-6.70 (m, 1.5H), 7.67 (s, 0.5H), 7.77 (d, J = 9.1 Hz, 0.5H).

Please replace the paragraph beginning on page 383, line 16 with the following paragraph:

To an aqueous solution of a mixture of 7-methoxymethoxy-2,2-dimethyl-6-nitro-2H-1-benzopyrane and the ~~positional isomer~~ regioisomer (1.5 g, 5.65 mmol) in dimethylsulfoxide (17 mL), N-bromosuccinimide (1.21 g, 6.78 mmol) was added at room temperature, and the resulting mixture was stirred for 3 hours. Upon the completion of the reaction, saturated ammonium chloride aqueous solution was added thereto, the resulting solution was extracted with ethyl acetate, washed with saturated sodium hydrogencarbonate aqueous solution and then with saturated sodium chloride solution, dried over magnesium sulfate, and concentrated. The resulting mixture was purified by silica gel column (hexane/ethyl acetate = 7/1) and the aimed product was obtained (yield: 27%).

Yellow solid

Please replace the paragraph beginning on page 385, line 4 with the following paragraph:

~~(±)-trans-6-amino-7-Methoxymethoxy-2,2-dimethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2H-1-benzopyran-3-ol~~ (±)-trans-6-Amino-7-methoxymethoxy-2,2-dimethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2H-1-benzopyran-3-ol

Please replace the paragraph beginning after page 385, line 17 with the following paragraph:

~~2-Chloro-N-[(±)-trans-3-hydroxy-7-methoxymethoxy-2,2-dimethyl-4-(2-phenylethylamino)-3,4-dihydro-2H-1-benzopyran-6-yl]-acetamide~~ 2-Chloro-N-[(±)-trans-3-hydroxy-7-methoxymethoxy-2,2-dimethyl-4-(2-phenylethylamino)-3,4-dihydro-2H-1-benzopyran-6-yl]-acetamide

Please replace the paragraph bridging pages 385 and 386 with the following paragraph:

~~To trans-6-amino-7-methoxymethoxy-2,2-dimethyl-6-amino-4-(2-phenylethylamino)-3,4-dihydro-2H-1-benzopyrane (242 mg, 0.65 mmol) in ethyl acetate-dimethylformamide mixed solution (5 mL), 4 M hydrogen chloride-dioxane solution (194 µL, 0.78 mmol) was added at 0°C, and the resulting mixture was stirred for 5 minutes. Chloroacetyl chloride (88 mg, 0.78 mmol) was added thereto, and the resulting mixture was stirred for 15 minutes. To~~ trans-6-amino-7-methoxymethoxy-2,2-dimethyl-6-amino-4-(2-phenylethylamino)-3,4-dihydro-2H-1-benzopyran (242 mg, 0.65 mmol) in ethyl acetate-dimethylformamide mixed solution (5 mL), 4 M hydrogen chloride-dioxane solution (194 µL, 0.78 mmol) was added at 0°C, and the resulting mixture was stirred for 5 minutes. Chloroacetyl chloride (88 mg, 0.78 mmol) was added thereto, and the resulting mixture was stirred for 15 minutes. Upon the completion of the reaction, ethanol and saturated sodium hydrogencarbonate aqueous solution were added thereto, the resulting solution was extracted with ethyl acetate, washed with saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The resulting mixture was purified by silica gel column (hexane/ethyl acetate = 1/1) and the aimed product was obtained (yield: 79%).

Pale pink oily product

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.17 (s, 3H), 1.45 (s, 3H), 2.75-3.00 (m, 4H), 3.43 (d, J = 9.9 Hz, 1H), 3.50 (s, 3H), 3.59 (d, J = 9.9 Hz, 1H), 4.20 (s, 2H), 5.19 (s, 2H), 6.61 (s, 1H), 7.15-7.30 (m, 5H), 8.14 (s, 1H), 8.73 (s, 1H).

MS (ESI<sup>+</sup>) m / z: 449 [M+1]<sup>+</sup>

MS (ESI<sup>-</sup>) m / z: 447 [M-1]<sup>+</sup>

Please replace the paragraph beginning on page 386, line 12 with the following paragraph:

~~2-Chloro-N-[(±)-trans-3,7-dihydroxy-2,2-dimethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2H-1-benzopyran-6-yl]-acetamide~~ 2-chloro-N-[(±)-trans-3,7-dihydroxy-2,2-dimethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2H-1-benzopyran-6-yl]-acetamide

Please replace the paragraph beginning on page 386, line 16 with the following paragraph:

To a solution of ~~2-chloro-N-[(±)-trans-3-hydroxy-7-methoxymethoxy-2,2-dimethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2H-1-benzopyran-6-yl]-acetamide~~ 2-chloro-N-[(±)-trans-3-hydroxy-7-methoxymethoxy-2,2-dimethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2H-1-benzopyran-6-yl]-acetamide (228 mg, 0.51 mmol) in methylene chloride (6 mL), boron tribromide (1 M solution in methylene chloride, 2.42 mL, 2.42 mmol) was added at 0°C, and the resulting mixture was stirred for 2 hours. Upon the completion of the reaction, methanol and saturated sodium hydrogencarbonate aqueous solution were added thereto, and the resulting solution was extracted with ethyl acetate, washed with saturated sodium hydrogencarbonate aqueous solution and then with saturated sodium chloride solution, dried over magnesium sulfate and concentrated to obtain the aimed product (yield: 100%).

Colorless amorphous product

MS (ESI<sup>+</sup>) m / z: 405 [M+1]<sup>+</sup>

MS (ESI<sup>-</sup>) m / z: 403 [M-1]<sup>+</sup>

Please replace the paragraph beginning on page 387, line 3 with the following paragraph:

To a solution of ~~2-chloro-N-[(±)-trans-3,7-dihydroxy-2,2-dimethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2H-1-benzopyran-6-yl]-acetamide~~ 2-chloro-N-[(±)-trans-3,7-dihydroxy-2,2-dimethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2H-1-benzopyran-6-yl]-acetamide (187 mg, 0.46 mmol) in methanol (2 mL), sodium hydroxide aqueous solution (1 mol/L, 1.8 mL) was added at room temperature, and the resulting mixture was stirred for 3 hours. Upon the completion of the reaction, saturated ammonium chloride aqueous solution was added thereto, the resulting solution was extracted with ethyl acetate, washed with 1 mol/L sodium hydroxide aqueous solution and then with saturated sodium chloride solution, dried over magnesium sulfate, and concentrated. The resulting mixture was purified by silica gel column (hexane/ethyl acetate = 1/3) and the aimed product was obtained (yield: 61%).

Colorless oily product

Please replace the paragraph beginning on page 387, line 19 with the following paragraph:

#### Synthesis Example 75

6,6-Dimethyl-8-(2-phenylethyl)amino]-2,3,7,8-tetrahydro-1H,6H-4,5-dioxa-1-aza-anthracene-7-ol 1-maleate



Please replace the paragraph beginning on page 388, line 1 with the following paragraph:

To (±)-*trans*-7-hydroxy-6,6-dimethyl-8-(2-phenylethylamino)-7,8-dihydro-1H,6H-4,5-dioxo-1-aza-anthracene-2-one (67 mg, 0.18 mmol), lithium aluminum hydride (1M solution in tetrahydrofuran, 910 µL, 0.91 mmol) was added at room temperature, and the resulting mixture was stirred at 90°C for 0.5 hour. Upon the completion of the reaction, saturated sodium hydrogencarbonate aqueous solution was added thereto, the resulting solution was extracted with ethyl acetate, washed with saturated sodium chloride solution, dried over magnesium sulfate, and concentrated. The resulting mixture was purified by silica gel column (ethyl acetate) and the aimed product was obtained (yield: 59%).

Colorless oily product

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.13 (s, 3H), 1.43 (s, 3H), 2.75-3.00 (m, 4H), 3.30-3.35 (m, 2H), 3.50-3.70 (m, 2H), 4.15-4.25 (m, 2H), 6.12 (s, 1H), 6.25 (s, 1H), ~~6.25 (s, 1H)~~, 7.20-7.35 (m, 5H).

MS (ESI<sup>+</sup>) m / z: 355 [M+1]<sup>+</sup>

MS (ESI<sup>-</sup>) m / z: 389 [M+45]<sup>+</sup>

Please replace the paragraphs beginning on page 388, line 16 with the following paragraphs:

(±)-*trans*-6,6-dimethyl-8-(2-phenylethylamino)-2,3,7,8-tetrahydro-1H,6H-4,5-dioxo-1-aza-anthracene-7-ol 1-maleate

To a solution of (±)-*trans*-6,6-dimethyl-8-(2-phenylethylamino)-2,3,7,8-tetrahydro-1H,6H-4,5-dioxo-1-aza-anthracene-7-ol in ethyl acetate (800 µL), maleic acid (14 mg, 0.12 mmol) was added at room temperature, and the resulting mixture was stirred for 10 minutes. Hexane (1 mL) was added thereto, and the resulting mixture was stirred at 0°C for 30

minutes. The resulting crystal was filtered off and the aimed product was obtained (yield: 73%).

Pale gray crystal

mp; ~~162-162°C~~ 160-162°C (decomposition)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.04 (s, 3H), 1.36 (s, 3H), 2.85-3.30 (m, 6H), 3.80-3.85 (m, 1H), 4.11 (d, J = 4.2 Hz, 2H), 4.15-4.20 (m, 1H), 6.05 (s, 2H), 6.18 (s, 1H), 6.76 (s, 1H), 7.20-7.40 (m, 5H).

Please replace the paragraph bridging pages 389 and 390 with the following paragraph:

Under nitrogen atmosphere, to a solution of 6-amino-2,2-dimethylchromene (3.88 g, 22.1 mmol) and ruthenium trichloride (55.0 mg, 0.265 mmol) in dimethylene glycol dimethyl ether (8 mL), 1,3-propanediol (0.639 mL, 8.84 mmol) and tri-n-butyl phosphine (0.132 mL, 0.530 mmol) were added at room temperature, and the resulting mixture was stirred at 180°C for 5 hours. Upon the completion of the reaction, ruthenium complex was removed by florisil column, and solvent was distilled off. The residue was purified by medium pressure column chromatography (hexane/ethyl acetate =5/1) and the aimed product was obtained (yield: 59%).

~~Gray~~ Brown amorphous product

<sup>1</sup>H-NMR(CDCl<sub>3</sub>); 1.49(s, 6H), 5.91(d, J = 9.9 Hz, 1H), 6.59(d, J = 9.9 Hz, 1H), 7.08(s, 1H), 7.24-7.28(m, 1H), 7.67(s, 1H), 7.93(d, J = 8.0 Hz, 1H), 8.70(dd, J = 4.1 Hz, 1.7Hz, 1H)  
MS(ESI+)m/z; 212 [M+1]<sup>+</sup>

Please replace the paragraph beginning on page 391, line 16 with the following paragraph:

This compound was synthesized according to the process of Synthesis Example 19.

(Yield: 30%)

Orange amorphous product

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.19 (s, 3H), 1.50 (s, 3H), 2.05-2.15 (br, 2H), 2.49 (s, 3H), 3.09-3.32 (m, 10H), 4.60-5.20 (br, 2H), 7.06 (s, 1H), 7.11 (s, 1H), 7.88 (s, 1H)

MS ( ~~$\text{EI}^+$~~ ) ( $\text{ESI}^+$ )  $m/z$ ; 390 $[\text{M}+1]^+$

Please replace the paragraph bridging pages 393 and 394 with the following paragraph:

To a solution of (3*R*\*,4*R*\*)-3-hydroxy-2,2,9-trimethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinoline-7-carbonitrile described in Synthesis Example 14 (465 mg, 1.20 mmol) in ethanol (5 mL), sodium hydroxide aqueous solution (3 mol/L, 5 mL) was added at room temperature, and the resulting mixture was stirred for 2 hours with reflux under heating. After cooling to room temperature, the resulting solution was neutralized with 1 mol/L hydrochloric acid, precipitated brown solid was filtered off and the aimed product was obtained (yield: 90%).

Brown solid

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.07 (s, 3H), 1.41 (s, 3H), 2.46 (s, 3H), 2.89-3.08 (br, 2H), 3.10-3.28 (br, 2H), 4.03-4.22 (br, 1H), 4.30-4.44 (br, 1H), 7.01-7.54 (m, 7H), 7.86 (s, 1H), 8.51-8.73 (br, 1H)

MS ( ~~$\text{EI}^+$~~ ) ( $\text{ESI}^+$ )  $m/z$ ; 407  $[\text{M}+1]^+$

Please replace the paragraph beginning after page 404, line 1 with the following paragraph:

~~(3*R*\*,4*S*\*)-7-chloro-2,2,9-trimethyl-6λ5-oxy-4-pentylamino-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinolin-3-ol hydrochloride~~ (3*R*\*,4*S*\*)-7-Chloro-2,2,9-trimethyl-6λ5-oxy-4-pentylamino-3,4-dihydro-2*H*-pyrano[2,3-*g*]quinolin-3-ol hydrochloride

(yield: 60%).

Pale yellow crystal

mp;226-230°C (decomposition)

<sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>) δ; 0.86(t, *J* = 6.3 Hz, 3H), 1.16(s, 3H), 1.27-1.29(m, 4H), 1.50(s, 3H), 1.60-1.72(m, 2H), 2.54(s, 3H), 2.86(brs, 1H), 3.07(brs, 1H), 4.07-4.10(m, 1H), 4.71(d, *J* = 8.5Hz, 1H), 6.51(d, *J* = 4.7 Hz, 1H), 7.47(s, 1H), 7.67(s, 1H), 9.04(s, 1H), 9.19(brs, 1H), 9.74(brs, 1H)

MS(ESI<sup>+</sup>)*m/z*; 379, 381 [M+1]<sup>+</sup>

MS(ESI)*m/z*; 423, 425 [M+45]<sup>+</sup>

Please replace the paragraph beginning on page 405, line 1 with the following paragraph:

To a solution of t-butyl (2-phenylethyl) (3*R*\*,4*S*\*)-7-amino-3-hydroxy-6-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl carbamate described in Synthesis Example 71 (1.04 g, 2.35 mmol) in pyridine (1.90 mL, 23.5 mmol), chloromethanesulfonylchloride (0.31 mL, 3.52 mmol) was added, and the resulting mixture was stirred at room temperature for 10 hours. Upon the completion of the reaction, 1 mol/L hydrochloric acid aqueous solution (ca. 30 mL) was added thereto to adjust pH to about 7, and then the resulting solution was extracted with ethyl acetate, washed with saturated sodium chloride aqueous solution, and dried over anhydrous sodium sulfate and concentrated. The resulting mixture was purified by

column chromatography (hexane/ethyl acetate = 3/1) and the aimed product was obtained (yield: 81%).

Colorless oily product

LC/MS (ES<sup>+</sup>) m/z: 555[M+1]<sup>+</sup>

LC/MS (ES<sup>-</sup>) m/z: 553[M-1]<sup>+</sup>

Please replace the paragraph bridging pages 405 and 406 with the following paragraph:

To a solution of (t-butyl (3*R*\*,4*S*\*)-7-[[chloromethyl)sulfonyl]amino}-3-hydroxy-6-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl (2-phenylethyl)carbamate (400 mg, 0.72 mmol) in dichloromethane (4.0 mL), 1 mol/L solution of boron tribromide in dichloromethane (3.61 mL, 3.61 mmol) was added below freezing point, and the resulting mixture was stirred at 0°C for 1 hour. Water was added, and the resulting mixture was further stirred for 30 minutes. The resulting solid was filtered off, washed with water and then with chloroform. The solid was dried at 60°C for 3 hours under reduced pressure, and the aimed product was quantitatively obtained.

LC/MS (ESI<sup>+</sup>) m/z: 441[M+1]<sup>+</sup>

LC/MS (ESI<sup>-</sup>) m/z: 439[M-1]<sup>+</sup>

Please replace the paragraph beginning on page 406, line 6 with the following paragraph:

To a solution of 1-Chloro-N-{(3*R*\*,4*S*\*)-3,6-dihydroxy-2,2-dimethyl-4-[(2-phenylethyl)amino]-3,4-dihydro-2*H*-1-benzopyran-7-yl} methanesulfonamide (220 mg, 0.50 mmol) in methanol (2.2 mL), 1 mol/L sodium hydroxide aqueous solution (1.00 mL, 1.00 mmol) was added, and the resulting mixture was stirred at room temperature for 3 hours.

Then, the temperature was raised to 50°C, and the mixture was further stirred for 2 hours.

Upon the completion of the reaction, the solution was cooled on standing, neutralized with saturated ammonium chloride aqueous solution, extracted 4 times with chloroform, and dried over anhydrous sodium sulfate. The solvent was distilled off and the aimed product was obtained (yield:37%).

Yellow solid

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.13 (s, 3H), 1.44 (s, 3H), 2.54 (brs, 3H), 2.79-3.02 (m, 4H), 3.49 (d, *J* = 10.0 Hz, 1H), 3.59 (d, *J* = 10.0 Hz, 1H), 4.86 (s, 2H), 6.23 (s, 1H), 6.78 (s, 1H), 7.21-7.35 (m, 5H)

LC/MS (ESI<sup>+</sup>) m/z: 405[M+1]<sup>+</sup>

LC/MS (ESI<sup>-</sup>) m/z: 403[M-1]<sup>+</sup>

Please replace the paragraphs bridging pages 407 and 408 with the following paragraphs:

Under nitrogen stream, a solution of N-benzyl-5-hydroxyisatin (4.74 g, 18.7 mmol), potassium iodide (5.09 g, 31.8 mmol), potassium carbonate (5.17 g, 37.4 mmol), copper iodide (71 mg, 0.37 mmol) and 3-chloro-3-methyl-1-butyne (4.83 mL, 43.0 mmol) in DMF (47 mL) was stirred at 70°C for 2 hours. Upon the completion of the reaction, saturated ammonium chloride aqueous solution was added thereto, the resulting solution was extracted with ethyl acetate. The resulting organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, concentrated and purified by silica gel short column (chloroform).

1,2-dichlorobenzene (9 mL) was added and the resulting mixture was stirred ~~at~~ at -200°C for 30 minutes. After concentrating the reaction solution, the residue was purified by silica gel column (hexane/ethyl acetate = 5/1) to obtain the aimed product (yield: 8%).

Red oily product

MS(ESI<sup>+</sup>)m/z; 320 [M+1]<sup>+</sup>

Please replace the table on page 414 with the following table:

| Synthesis   | Dose (mg/kg) | Atrial Refractory Period |
|-------------|--------------|--------------------------|
| Example No. | (mg/kg)      | (msec)                   |
| 2           | 0.6          | 21                       |
| 4           | 0.6          | 30                       |
| 6           | 0.6          | 20                       |
| 7           | 0.6          | 25                       |
| 8           | 0.6          | 23                       |
| 14          | 0.3          | 27                       |
| 18          | 0.3          | 27                       |
| 19          | 0.3          | 26                       |
| 23          | 0.3          | 22                       |
| 24          | 0.3          | 23                       |
| 25          | 0.3          | 27                       |
| 26          | 0.3          | 24                       |
| 27          | 0.3          | 32                       |
| 41          | 0.3          | <del>21</del> <u>31</u>  |
| 47          | 0.3          | 24                       |
| 48          | 0.3          | 23                       |
| 52          | 0.3          | 28                       |
| 53          | 0.3          | 30                       |
| 58          | 0.3          | 28                       |

|    |                           |    |
|----|---------------------------|----|
| 59 | 0.3                       | 22 |
| 60 | 0.3                       | 22 |
| 61 | 0.3                       | 20 |
| 63 | 0.3                       | 23 |
| 69 | 0.3                       | 37 |
| 71 | 0.3                       | 31 |
| 73 | 0.3                       | 31 |
| 74 | <del>0.3</del> <u>0.6</u> | 25 |
| 77 | 0.3                       | 25 |